

ORSETT BRIEFING PAPERS FOR PSYCHOLOGISTS

No.2 - Basic Genetics

The Cell

Each cell in the body contains a complete set of chromosomes. The chromosomes are numbered 1 to 22 in humans based on decreasing size. Chromosomes are spread in two ways.

The first process of cell division is known as mitosis. The new cell contains the exact duplication of pairs of chromosomes as the original.

While in the process of meiosis, the gametes (matured sex cells; ie: sperm or egg) receive half the pair of chromosomes of the parent. Thus during reproduction the pair of chromosomes are reformed from the mother and father's gametes.

However, one chromosome does not follow these rules - the X chromosome. This chromosome can have two forms: XX (which determines a female) or XY (for male).

The chromosome complement is known as a karyotype, which for humans is 46: 22 pairs (known as autosomes) the same for either sex and then XX or XY.

On occasions, there can be extra copies of a chromosome (known as trisomy) eg Down's syndrome and trisomy 21 (an extra copy of chromosome 21). Other chromosomal abnormalities include deletions or duplications of part of a chromosome.

Chromosomes

Chromosomes are made up of genes, which are based on DNA (deoxyribonucleic acid). DNA is made up of four bases: adenine (A), guanine (G), cytosine (C), and thymine (T). These are ordered around two chains wrapped together as the double helix.

The nature of DNA is such that A always pairs with T, and C and G. The sequence of bases is the genetic information.

Genetic information is transported within the cell by messenger ribonucleic acid (mRNA). Each molecule of mRNA contains a molecule of DNA (this process is transcription), and mRNA is translated into proteins. The proteins are, for example, leucine, glycine, and arginine. These are, simplistically, the building blocks for the physical manifestation of the gene's instructions. More details of these processes are being discovered all the time.

Inheritance

Changes in the sequence of bases leads to changes in cell development. Point mutation is the substitution of one base for another, and is the most obvious example. Others include deletions (loss of sequence of bases), insertions (gaining of a piece of DNA) ¹, frameshift mutations (the loss of one base affecting the coding of others), and translocations (the breaking of part of a chromosome and reforming at a different site on a different chromosome) (figure 1). These changes can be advantageous in the evolutionary sense as well as disadvantageous.

NORMAL SEQUENCE	ACCGTTTTA
DELETION	ACCGTTT..
POINT MUTATION	ACCGATTTA
INSERTION	ACCTTGTTG

Figure 1 - Examples of changes in sequence of bases.

Comparison of sequences of DNA or repeated sequences (known as tandem repeats) can be used to compare genetically related individuals, and to pinpoint the genetic basis of behaviour.

Genes produce a phenotype (manifestation of behaviour based on genetic make-up and environment), and are viewed as dominant or recessive. Dominant genes require only one copy from either parent to manifest the behaviour (phenotype), while both copies are needed for recessive genes to show the behaviour. Individuals with one copy of a recessive gene are known as carriers. There are a number of possibilities for the offspring (figures

¹ Eg: Fragile X syndrome and the X chromosome. Normally there are between 6-50 copies of the sequence CCG, but in fragile X, there are between 230-2000 copies of the sequence. This is an example of a disorder associated with expanded triplet repeat.

2 and 3).

Genetic traits can be inherited together over a number of generations because genes are close together on the same chromosome. This is known as linkage disequilibrium. This fact is one that has helped in the modern development of molecular biology.

PARENT A	PARENT B	OFFSPRING
DD	DD	All DD
RR	RR	All RR
DD	RR	All DR; ie: express D but carry R
DD	DR	All express D but carry R
RR	DR	All carry R but express D
DR	DR	3/4 express D; 1/4 express R; 2/3 carry R

D = dominant gene; R = recessive gene

Figure 2 - Possible relationships of dominant and recessive genes

PARENT A	PARENT B	OFFSPRING
RR	NN	All RN (carrier)
RN	NN	1/2 RN; 1/2 NN (normal)
RN	RN	1/4 RR (affected); RN; 1/4 NN
RN	RR	1/2 RR; 1/2 RN

R = recessive gene; N = normal gene

Figure 3 - Example of recessive gene and inheritance.

Another important discovery concerns restriction enzymes. These substances are found to cut DNA where specific base sequences occur, and to divide the DNA into "manageable chunks". This is very important in "molecular cloning". The major developments in studying genes are based around better ways of spotting base sequences in such a mass of information.

Studying Genetics

The study of genetics often makes use of "genetic markers". The term "genetic marker" usually means an inherited characteristic which is stable over time, and thus can be reliably detected across generations. "Classical" markers include blood group, histocompatibility (HLA) antigens, and colour blindness ².

There are also "DNA markers" called "restriction fragment length polymorphisms" (RFLP) or restriction enzymes (linked to alterations in the base sequences).

For example, BamHI (a protein of bacterial origin) recognises the following six base pair sequence by cleaving to that sequence:

```
  G  G  A  T  C  C
  C  C  T  A  G  G
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The steps in the process using RFLPs is as follows:

1. Isolate DNAs from blood, for example.
2. Cutting of DNA into manageable chunks with restriction enzymes.
3. Separate double-strand fragments of DNA into single ones (a process known as denaturation).
4. Transfer the fragments of DNA to nylon membrane and prepare for analysis. This last step becomes very technical.

It is possible to use genetic markers to distinguish specific alleles (possible copies). The markers may not be related to the mutation in the DNA, but are known to be close to it. Simply, the aim is to find a variant in the DNA in affected members of a family, but not in unaffected members. It is usually assumed that the marker is close enough to the pathological gene on the same chromosome that separation during meiosis (recombination) is unlikely.

The frequency of recombination is used as a measure of the physical distance separating two loci (positions). A statistical assessment of the likelihood of linkage between two loci is calculated as a lod (log of odds that two loci are linked) score ³. A score of 3 or more is accepted as evidence of linkage in Mendelian transmission

² Linkage has been reported between schizophrenia and a number of markers, like immunoglobulin proteins, Gm and Bc, and phosphoglucomutase (Gurling, Read and Potter 1991).

³ Morton, N.E (1955) Sequential tests for the detection of linkage, American Journal of Human Genetics, 7, 277-318.

(ie: single gene involved) ⁴.

The process of searching for a gene can be random, or using a candidate gene (a suspected gene: eg dopamine D2 receptor for schizophrenia). The detailed mapping of the Human Genome Project has meant there is less "shooting in the dark". All of the techniques so far are based on searching for a single gene (known as Mendelian transmission). But, in many cases, there will be multiple genes (polygenic) involved.

Methods of Studying Genetics

1. Association studies

This method seeks to compare genes in ill patients with healthy individuals in the general population. Genes that appear more frequently with the patients are seen as associated with the illness.

2. Linkage studies

Based on families with an illness, this type of study segregates family members with or without the illness. It is possible to focus upon a particular loci (position on chromosome), and to see which allele exists there for ill family members as opposed to healthy ones.

At any given genetic locus (position), there are two alleles (copies) of the DNA sequence. One of the alleles is from the mother, and one from the father. The aim is to focus on specific regions of a chromosome.

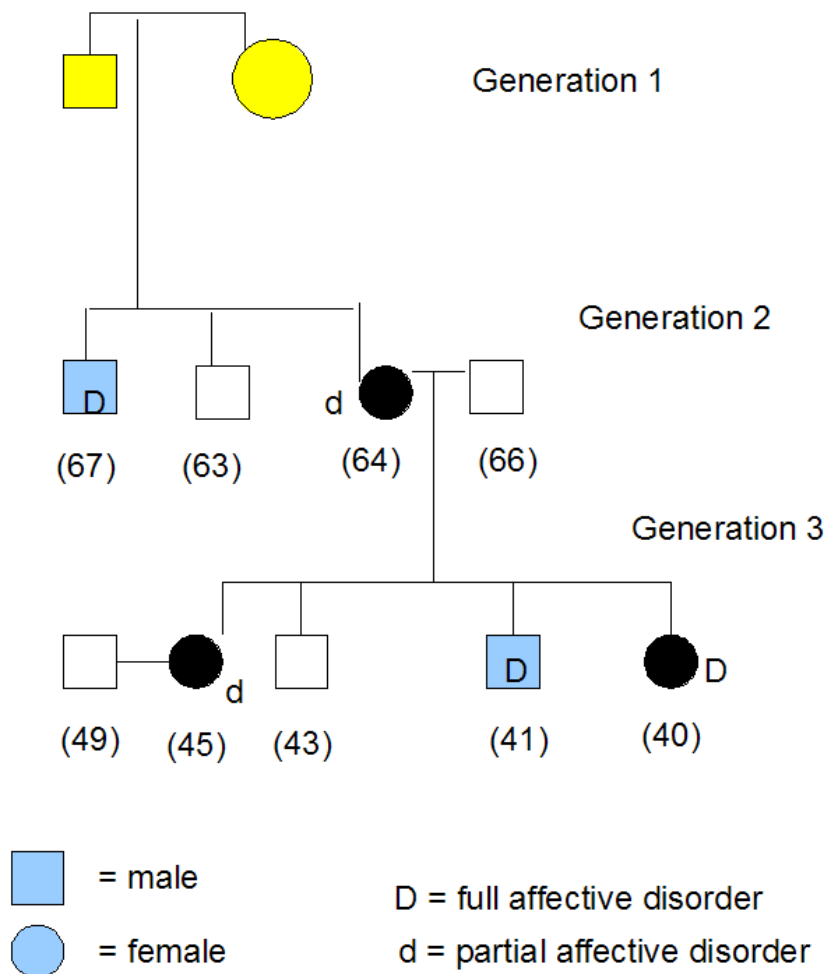
An example of linkage study is shown in figure 4. This is based upon the use of glucose-6-phosphate dehydrogenase (G6PD) deficiency as the marker for affective disorder (Mendlewicz et al 1980). This marker is carried on the X chromosome, and is recessive. Males with the marker are affected, while carrier females are mothers of affected males.

3. Segregation analysis

This method aims to show whether the pattern of illness in a family is linked to a specific mode of transmission (ie: related to specific gene or genes) ⁵

⁴ A well-known example of this situation was the discovery, in 1983 by a team led by James Gusella, of a close genetic linkage between Huntington's disease and a DNA marker on the short arm of chromosome 4.

⁵ Elston, R.C & Stewart, J (1971) A general model for the analysis of pedigree data, Human Heredity 21, 523-542.



Blue = G6PD deficiency

Black = carrier of G6PD deficiency

White = no G6PD or carrier

Yellow = status unknown because dead

() = age

Figure 4 - Example of pedigree as used in linkage studies like Mendlewicz et al (1980).

An estimate of the likelihood of a particular mode of transmission is produced.

There are a number of limits with this method:

- i) Variable penetrance - some individuals with the genetic predisposition will not show the disease.
- ii) Phenocopies - individuals without the genetic predisposition who show symptoms of the disease.
- iii) Genetic heterogeneity - the same symptoms can be produced by more than one type of genetic cause.

Genetic Mechanisms

Most diseases are complex and not linked to single genes. There are a number of genetic mechanisms involved⁶:

i) Epistasis - this is the interaction of multiple genes to produce the illness. This process is known to be the cause of retinitis pigmentosa (progressive degeneration of the retina).

ii) Locus heterogeneity - this is where multiple genes are involved, but any one gene can produce the illness on its own also. Retinitis pigmentosa is linked to 14 different loci (gene positions).

iii) Allelic heterogeneity - there are multiple alleles at a single disease locus. This is a number of possible genes at one particular situation, and a certain combination produces the illness.

iv) Dynamic mutation - here at a single disease locus, the allele mutates between generations. A particular gene mutates between parents and offspring. This is the case for Huntington's chorea.

v) Parent of origin effect - the expression of the allele depends upon the parental origin. The gene at a particular locus from the biological father will have a different effect to that from their biological mother.

The absence of maternal chromosome 15 (q11-13) leads to Angelman syndrome (eg: spasms, "puppet-like" movements, and low intelligence), while absence of the paternal version causes Prader-Willi syndrome (which includes the symptoms of obesity and low intelligence).

vi) Mitochondrial gene mutation - the illness is linked to the maternal pattern of inheritance as genes in the mitochondria are only inherited from the mother. This mechanism may be involved in some forms of deafness.

⁶ Craddock, N & Owen, M.J (1996) Modern molecular genetic approaches to psychiatric diseases, British Medical Bulletin, July, 434-452.

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